GENETICS AND GENOMICS OF EXCEPTIONAL LONGEVITY

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BACKGROUND

- Longevity is a polygenic trait influenced by genes and environment
- Heritability is 15–40%
- Diet and lifestyle are more important than genetics in middle age to early old age
- Genetic factors are more important for reaching 90+ years of age
- Genetic variants that reduce the risk of diseases of ageing (cardiovascular disease, cancer, diabetes, neurological disorders, etc) are associated with increased lifespan

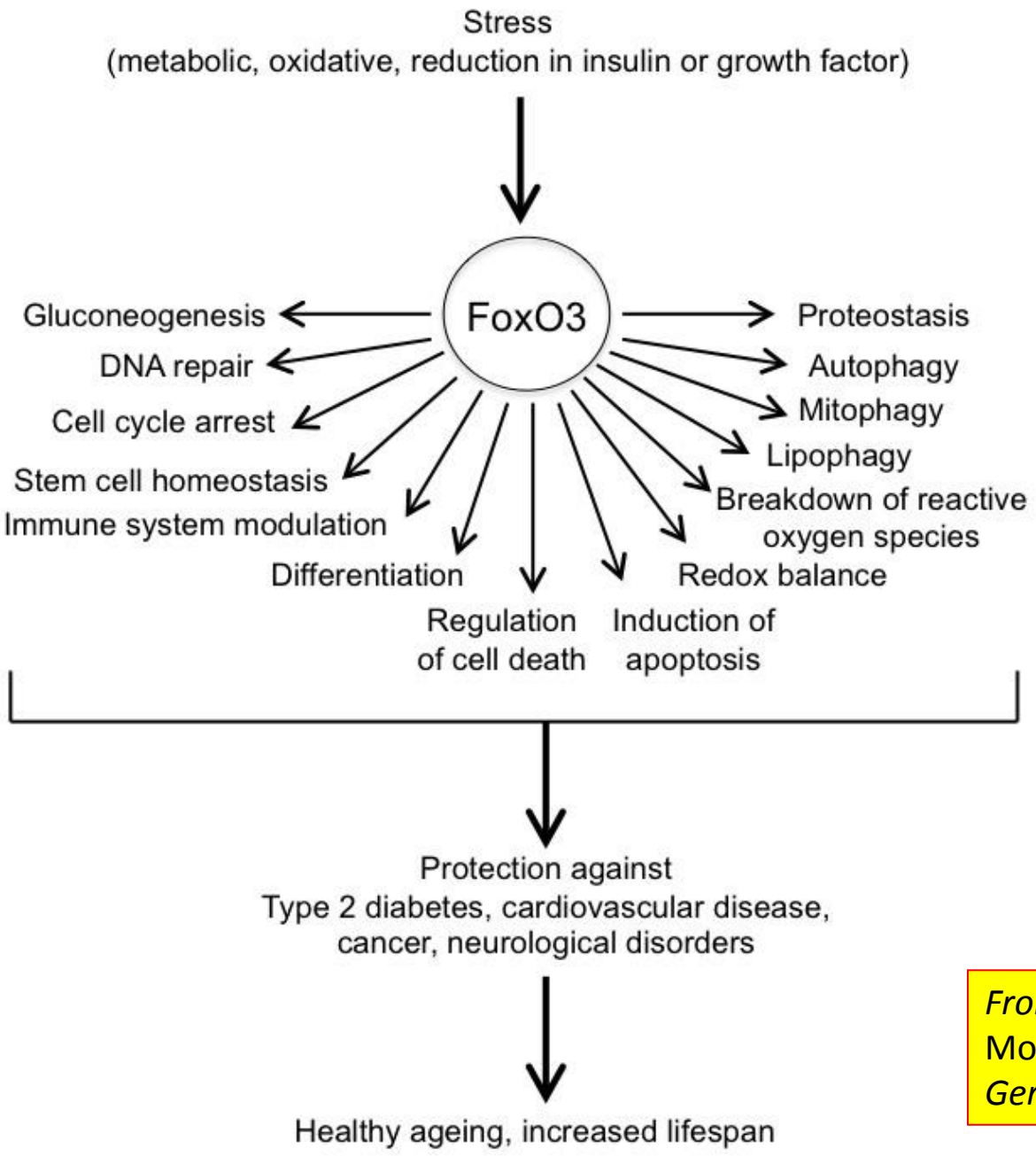
CASE-CONTROL STUDIES

- Long-lived subjects vs. normal lifespan subjects
- Compare frequency of genotypes for single nucleotide polymorphisms (SNPs) in potential candidate longevity genes
- Test for association with longevity

TOMM40/*APOE*/*APOC1* cluster

- *APOE* has 3 common alleles: ε2, ε3 and ε4
- ε4 has a survival advantage at younger ages, but increased risk of cardiovascular disease and Alzheimer's later in life (antagonistic pleiotropy)
- ε4 ⟶ ↑cholesterol, LDL-C, apolipoprotein B, lipoprotein(a), atherosclerosis, body mass index
- Attrition of ε4 carriers from early death ⟶ ↑ε2 in the population of survivors
- Multiple genetic variants in the *TOMM40*/*APOE*/*APOC1* locus influence expression of these genes

FOXO3



From mini-review:
Morris *et al.*, *Gerontology* 2015

THE STUDY POPULATION IN HAWAII

- 8,006 middle-aged Japanese-American men were recruited in 1965–68 for the Honolulu Heart Program and followed ever since
- > 1200 of these reached 90+ years of age and > 800 reached ≥ 95+ years
- 3,584 were alive in 1991–93 (baseline)

The Hawaii Lifespan Studies I and II NIA R01s: Defining the Healthy Aging Phenotype (I) and Genotype (II)

Japanese-American centenarian, age 101 years

NOTABLE CHARACTERISTICS OF LONG-LIVED SUBJECTS

Well-known risk factors significantly lower:

fasting plasma glucose
fasting plasma insulin
plasma fibrinogen
white blood cell count
smoking history
difficulty walking 0.8 km
taking diabetes medication
coronary artery disease
stroke history
cancer, diabetes, emphysema
bypass history, angioplasty, cardiovascular surgery
ankle-brachial index.

Protective factors higher:

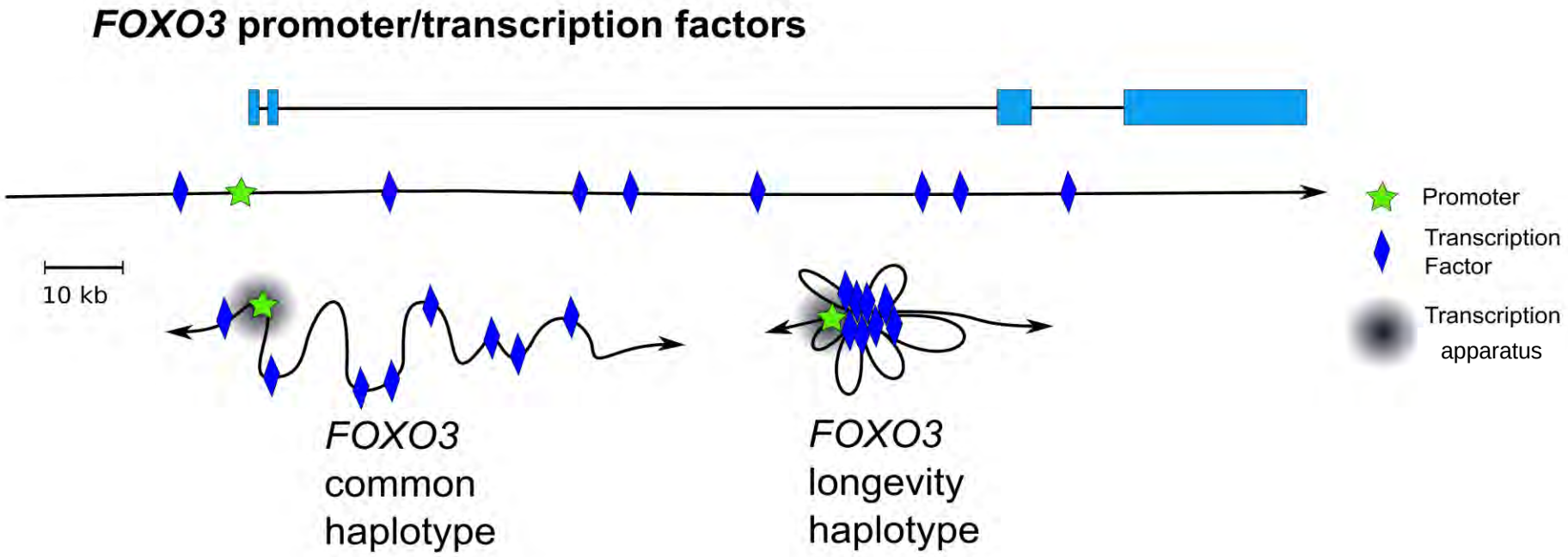
expiratory volume
grip strength
cognitive score
being married.

We found 41 *FOXO3* SNPs are associated with longevity

13 of these affected binding sites of 18 transcription factors

The transcription complex formed is 'tighter' for the haplotype involving SNPs associated with longevity

(for simplicity only 8 of the 18 transcription factor binding sites are shown below)



So stronger *FOXO3* expression

FOXO3

- Encodes a transcription factor in the insulin/IGF-1 signalling pathway
- Association with longevity highly replicated
- *G* allele of SNP *rs2802292* is strongest
- ⟶ 36% ↑ in likelihood of living to ≥ 95 years
- *G* allele creates binding site for HSF1
  ⟶ ↑ resilience to stress ⟶ longevity

Grossi *et al.* *NAR* 2018

- ↓ inflammation, no telomere attrition,
  ↓ risk of death from coronary heart disease

Willcox *et al*. *PNAS* 2008, *Aging Cell* 2016; Donlon *et al*. *Aging Cell* 2017

OTHER GENES

We tested 459 SNPs in 47 human homologues of mouse genes differentially expressed in mouse liver in response to caloric restrictions

Gene	±Fold-change	Gene	±Fold-change	Gene	±Fold-change
APEX1	–1.3	*FOXO3*	+1.5	*NR3C1*	–1.5
APTX	–2.3	*GCLC*	–2.0	*PDPK1*	+1.3
AR	–2.8	*GCLM*	–1.5	*PIK3R1*	–1.4
ARHGAP1	–1.3	*GHR*	–2.1	*PLAU*	+2.7
BLM	+4.7	*GSTA4*	–1.7	*PPARA*	–2.3
CDKN1A	+10.2	*HSPA8*	+1.6	*PPARGC1A*	+6.0
CEBPA	–1.6	*IGFALS*	–2.4	*SGK1*	+4.6
CEBPB	+2.2	*JAK2*	–1.4	*SNCG*	–2.0
CEBPD	+4.3	*JUN*	+2.1	*STAT3*	+1.7
CTGF	+3.3	*LEPR*	+58.4	*TERT*	–2.9
CTSL	+4.9	*LMNB1*	–1.5	*TFDP1*	–1.3
DDIT4	+33.3	*MAP3K5*	+2.0	*TOP2A*	–1.5
EGFR	+1.7	*MAPK3*	–1.2	*TXN*	–1.5
ERCC3	–1.3	*MAPK9*	–1.3	*VCP*	–1.3
FLT1	+1.4	*NFKBIA*	+1.5	*XRCC5*	–1.3
FOXO1	+1.5	*NNMT*	+36.5		

We have also tested SNPs in 20 other genes of interest

Insulin/IGF-1 pathway genes:
ATF4, *CBL*, *CDKN2*, *EXO1*, *JUN*
[Morris *et al. JGBS* 2014]

TOR complex genes:
MTOR, *RPTOR*, *RICTOR*, *RPS6KA1*
[Morris *et al. JGBS* 2015]

Sirtuin genes:
SIRT1, *SIRT2*, *SIRT3*, *SIRT4*, *SIRT5*, *SIRT6 SIRT7*
[Donlon *et al. JGBS* 2016]

Others:
FAS, *LMNA, APOE/TOMM40*

STRONGEST GENE ASSOCIATIONS WITH LONGEVITY IN OUR COHORT

Growth factor genes
12 SNPs in *CTGF*; 7 SNPs in *EGFR*
[Donlon *et al. JGBS* 2016]
Vascular endothelial growth factor receptor gene: *FLT1* haplotype
[Donlon *et al. JGBS* 2018]

Sirtuin genes
SIRT7, *SIRT5*
[Donlon *et al. JGBS* 2018]

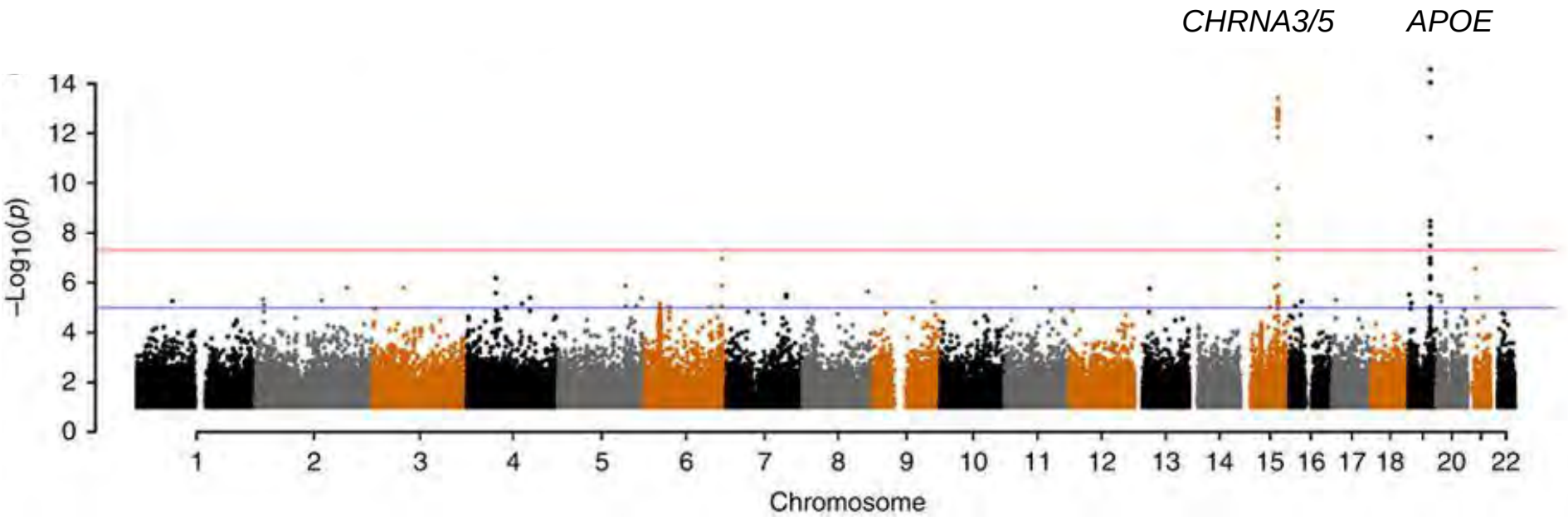
Kinase genes
Mitogen activated kinase kinase kinase gene: *MAP3K5*
Phosphoinositide-3-kinase regulatory subunit 1: *PIK3R1* haplotypes
[Donlon *et al. JGBS* 2018]

GENES IMPLICATED IN ASSOCIATION STUDIES BY OTHERS

Angiotensin converting enzyme gene: ***ACE***
BPIFB4 Ile229Val polymorphism – vascular effects
KLOTHO G–395A promoter polymorphism
Thioredoxin reductase gene: ***TXNRD1***
Superoxide dismutase 3 gene: ***SOD3***
AKT serine/threonine kinase 1 gene: ***AKT1***
Mitochondrial DNA **haplogroups H, J, K**
Cholesterol ester transfer protein gene: ***CETP***
Syndecan-4 gene: ***SDC4***
Interleukin-10 gene: ***IL10***
Major histocompatibility complex class II gene: ***HLA-DQB1***
Inflammation and DNA repair gene locus: ***RAD50***/***IL13***
Genes involved in DNA repair: ***LMNA***, ***WRN***, ***CDKN2A***, ***CDKN2B***
Aldehyde dehydrogenase 2: ***ALDH2***
Proprotein convertase/kexin type 1 gene: ***PCSK1***
V-yes-1 Yamaguchi sarcoma viral related oncogene homolog: ***LYN***
Solute carrier family 1 member 5 gene: ***SLC1A5***
Sirtuin 2 gene: ***SIRT2***
Dopamine receptor 2 gene: ***DRD2***
Serpin family E member 1 gene (encoding plasminogen activator inhibitor-1): ***SERPINE1***
Fibronectin type III domain-containing 5 gene: ***FDNC5***
Vitamin D receptor gene: ***VDR***

GENOME WIDE ASSOCIATION STUDIES OF LONGEVITY

Example



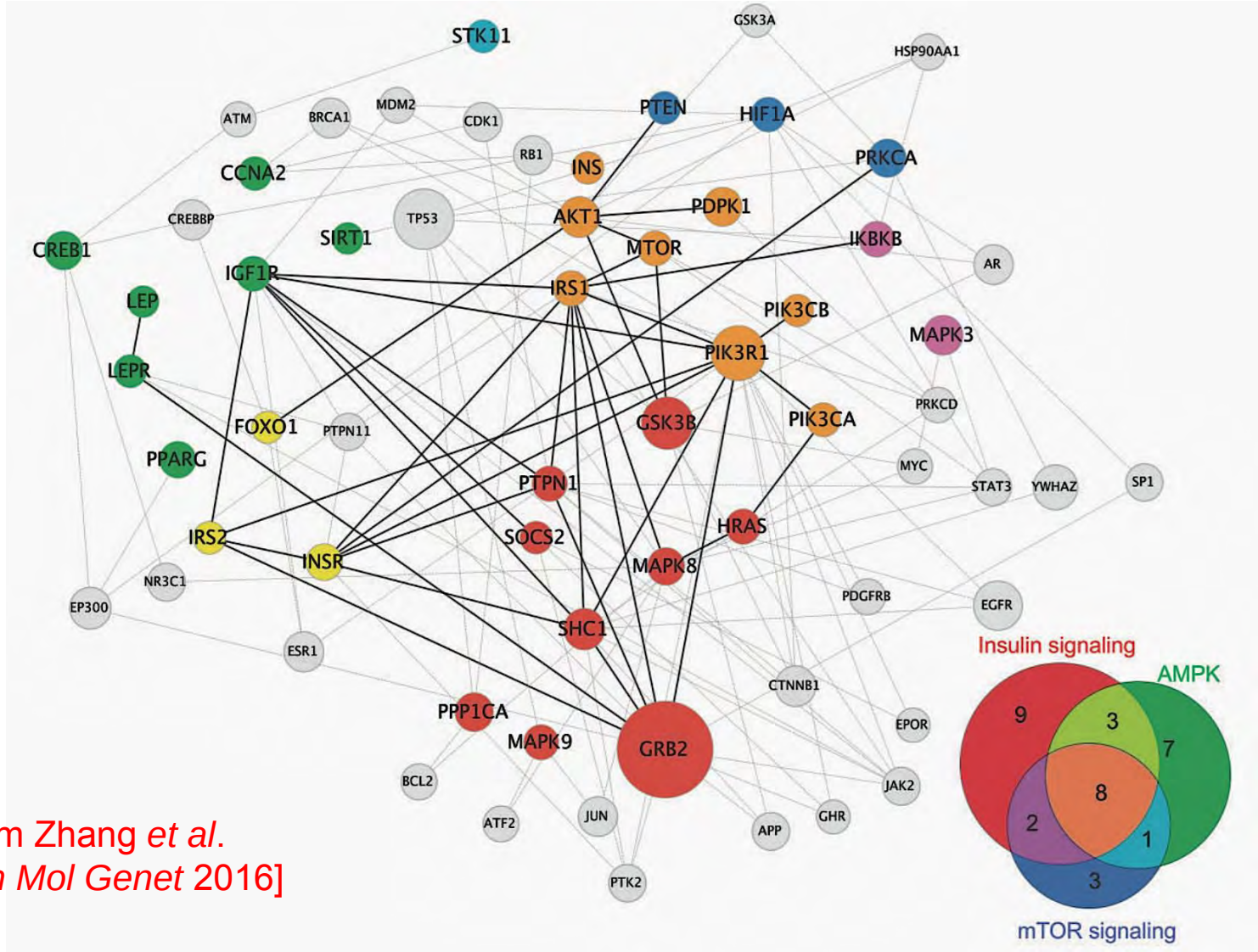
Summary of results of all genome wide association studies

~57 loci associated with longevity

Chr1: *NBPF6*, *NBPF5*, *CLESR2*…*PSRC1*, *FPGT*/*TNNI3K*
Chr2: *CAPN9*, *C1ORF*
Chr3: *TOP2B*
Chr4: *ELOVL6*
Chr6: *BMP5*, *PLG*/*MAP3K5*, *PARK2*, *FOXO3*, *LPA*, *HLA-DRB1*…*HLA-DQA1*, *BEND3*, *PSORS1C3*…*MICA*…*MICB*
Chr7: *AP5Z1*, *IL6*, *USP42*
Chr8: *EPHX2*, *TOX*
Chr9: *TLR4*, *DBC1*, *C9orf62*, *CDKN2B-AS1* (*ANRIL*)
Chr10: *KLF6*
Chr11: *ZW10* (male), *USP2-AS1*
Chr12: *TMTC2*, *SH2B3*/*ATXN2*
Chr13: *ANKRD20A9P*, *B3GALTL* (female),
Chr14: no gene assigned
Chr15: *CHRNA3*, *CHRNA5*, *FURIN*, *SEMA6D*
Chr17: no gene assigned
Chr18: *SMAD7*, *MC2R*
Chr19: *TOMM40*/*APOE*/*APOC1*, *EGLN2*…*CYP2A6*, *EXOC3L2*
Chr20: *C20orf187*, *CHRNA4*

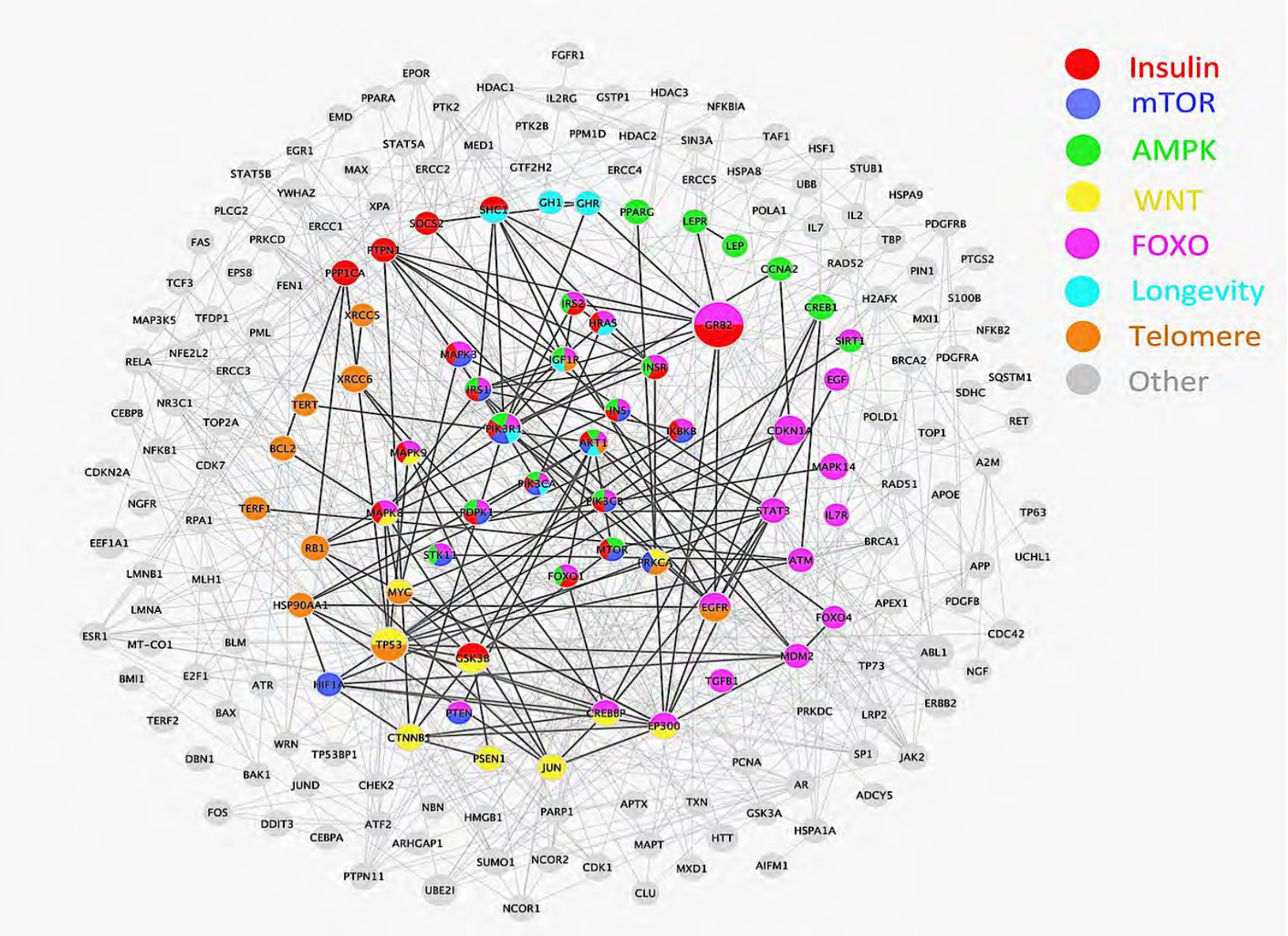
THE "GERONTOME"

Aging-related **protein interaction** subnetwork for three well-known aging-related pathways: insulin signalling, AMPK and mTOR signalling



[From Zhang *et al*. *Hum Mol Genet* 2016]

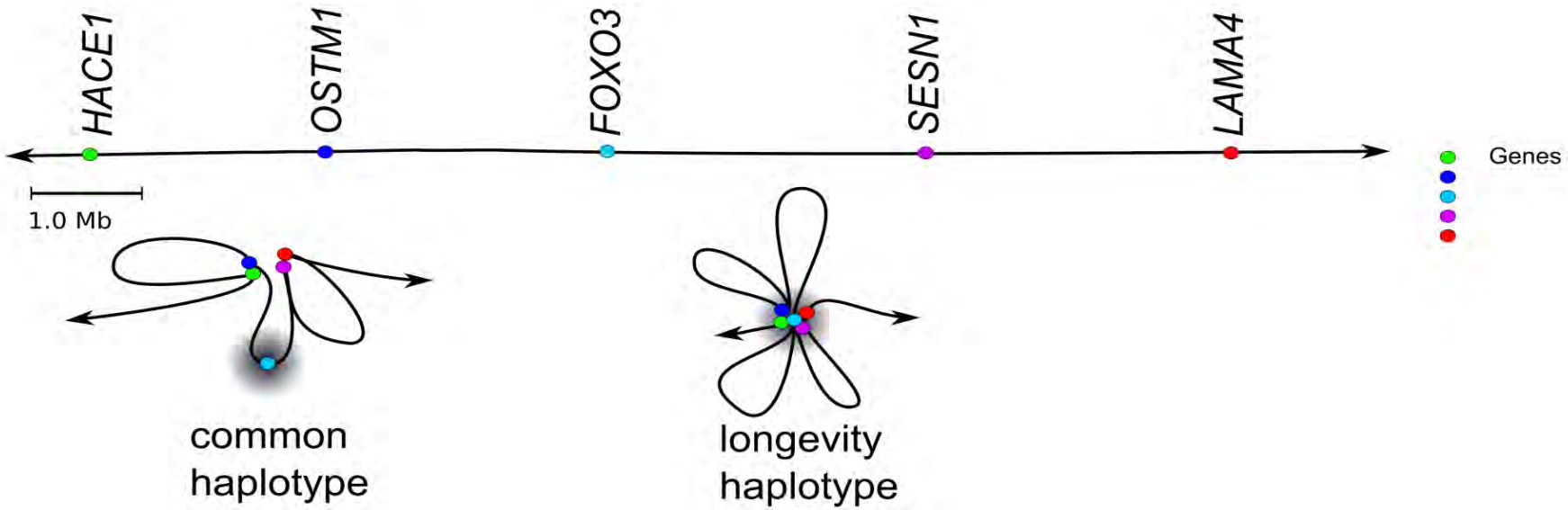
The ageing subnetwork consists of 192 proteins encoded by ageing-related genes and 561 direct interactions among these proteins



A GENE NEIGHBOURHOOD INVOLVED IN LONGEVITY

How *FOXO3* haplotype might influence chromatin conformation and expression of 46 neighbouring genes on chromosome 6q21 via long-range interactions

(for simplicity only 4 of the 46 genes are shown)



Involves direct gene-gene interactions

- We identified distant contact points between *FOXO3* and 46 neighbouring genes, including *HACE1*, *BVES*, *AIM1*, *SCML4*, *CD164*, *AK9*, *FIG4*, *WASF1*, *SLC22A16*, *RPF2*, *FYN*, *WISP3*, *TUBE1* and *LAMA4*, through long-range physical contacts via CCCTC-binding factor zinc finger protein (CTCF) binding sites, over a 7.3 Mb distance on chromosome 6.

"*FOXO3* INTERACTOME"

- *Cis*-regulatory elements are brought together into co-regulated islands and multiple islands are brought together into a functional neighbourhood (or "archipelago") by chromatin looping.

- The 7.2 Mb region is flanked by gene deserts.

Donlon *et al*. *Aging Cell* 2017

The neighbourhood genes have overlapping functions and similar expression patterns as *FOXO3*

- autophagy (HACE1, ATG5, SOBP, SEC63, FIG4)
- energy sensing (OSTM1)
- stress response (SNX3)
- nutrient sensing (SESN1)
- cell proliferation (CD164)
- apoptosis (MICAL1)
- cell proliferation (CDC40, RPF2, FYN, TUBE1, GTF3C6)
- stem cell maintenance (AMD1)

HUMAN LONGEVITY 'GENE FACTORY'

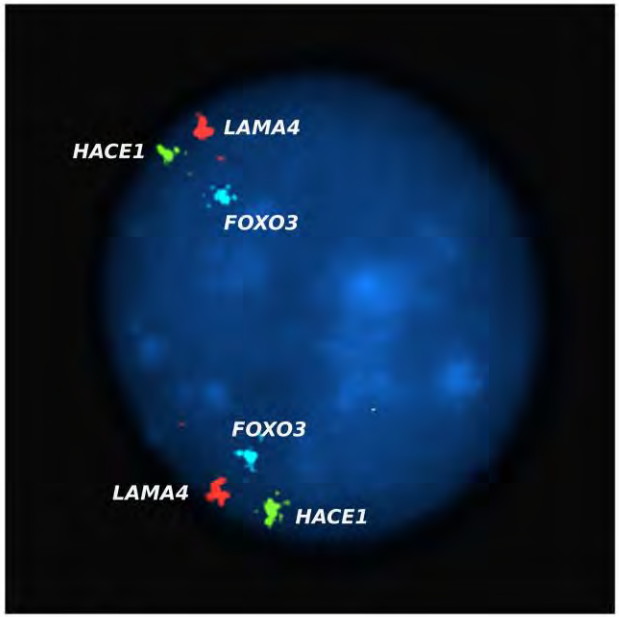
EXPERIMENTAL VALIDATION

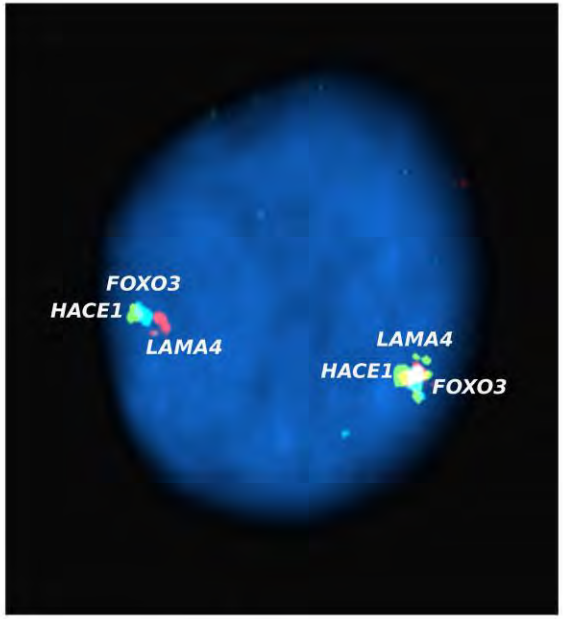
- Culture of lymphoblastoid cell lines from 20 offspring of long-lived subjects:
  - 10 cell lines with protective minor *G* allele of SNP *rs2802292*
  - 10 cell lines with common *T* allele of SNP *rs2802292*

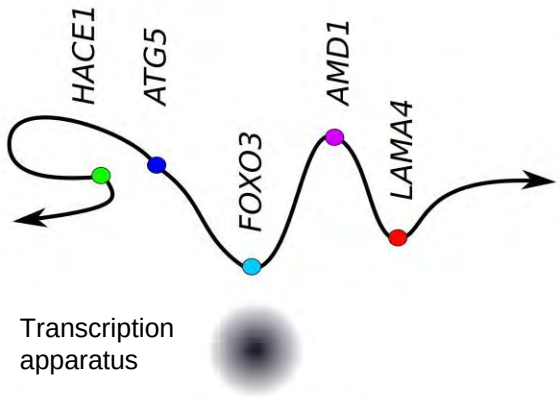
- ± Stress (200 μM hydrogen peroxide + serum deprivation)

- Perform fluorescence in situ hybridization

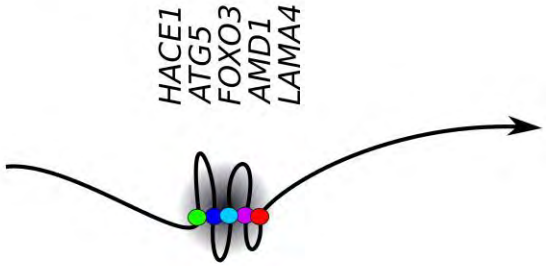
- Measure changes in relative position of *FOXO3* and genes flanking it





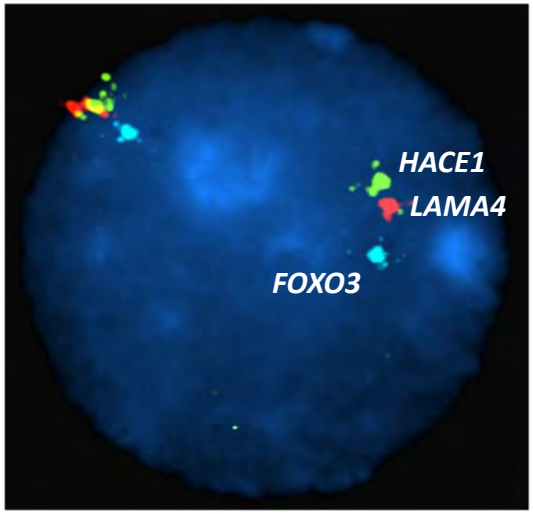


Quiescent

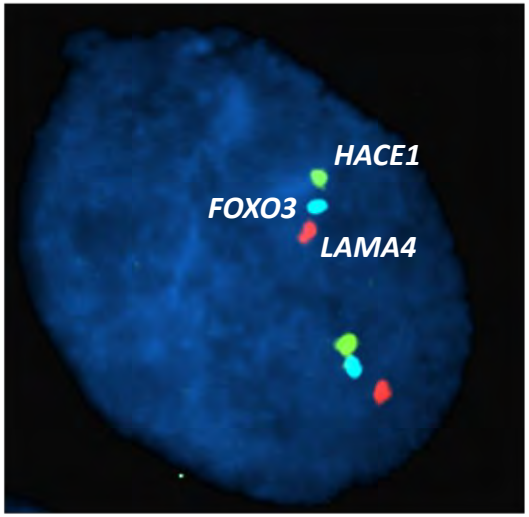


Stressed

Stress (hydrogen peroxide) caused the genes to cluster in fibroblast cell lines from long-lived subjects. Stronger for *FOXO3 G*-allele carriers

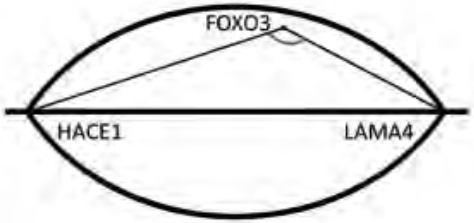


resting



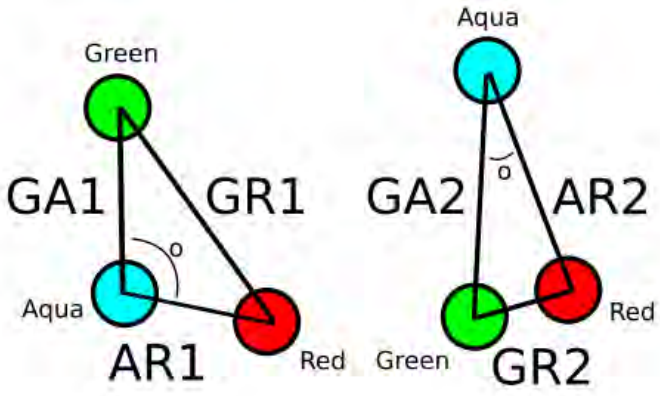
stressed

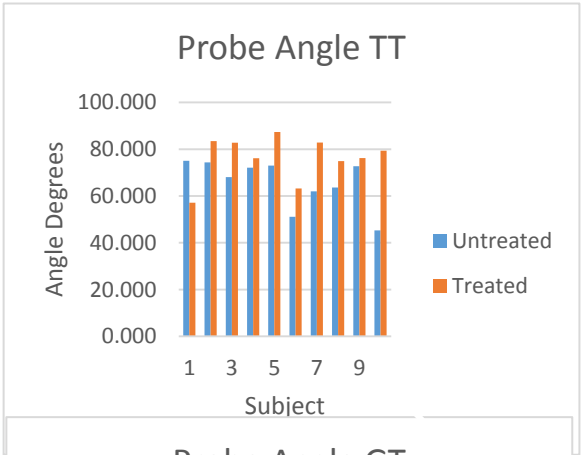
FISH probes

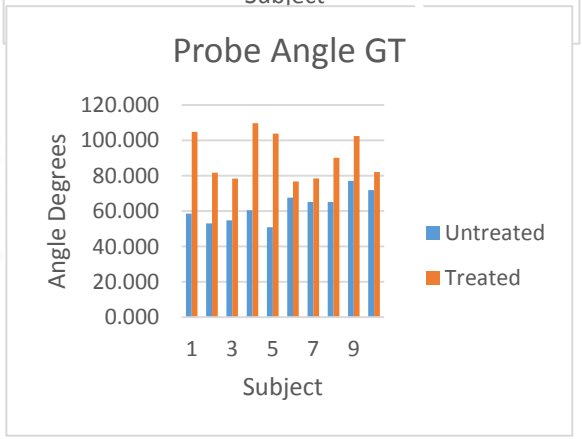


Stress → ↓ Distance and ↑ angle

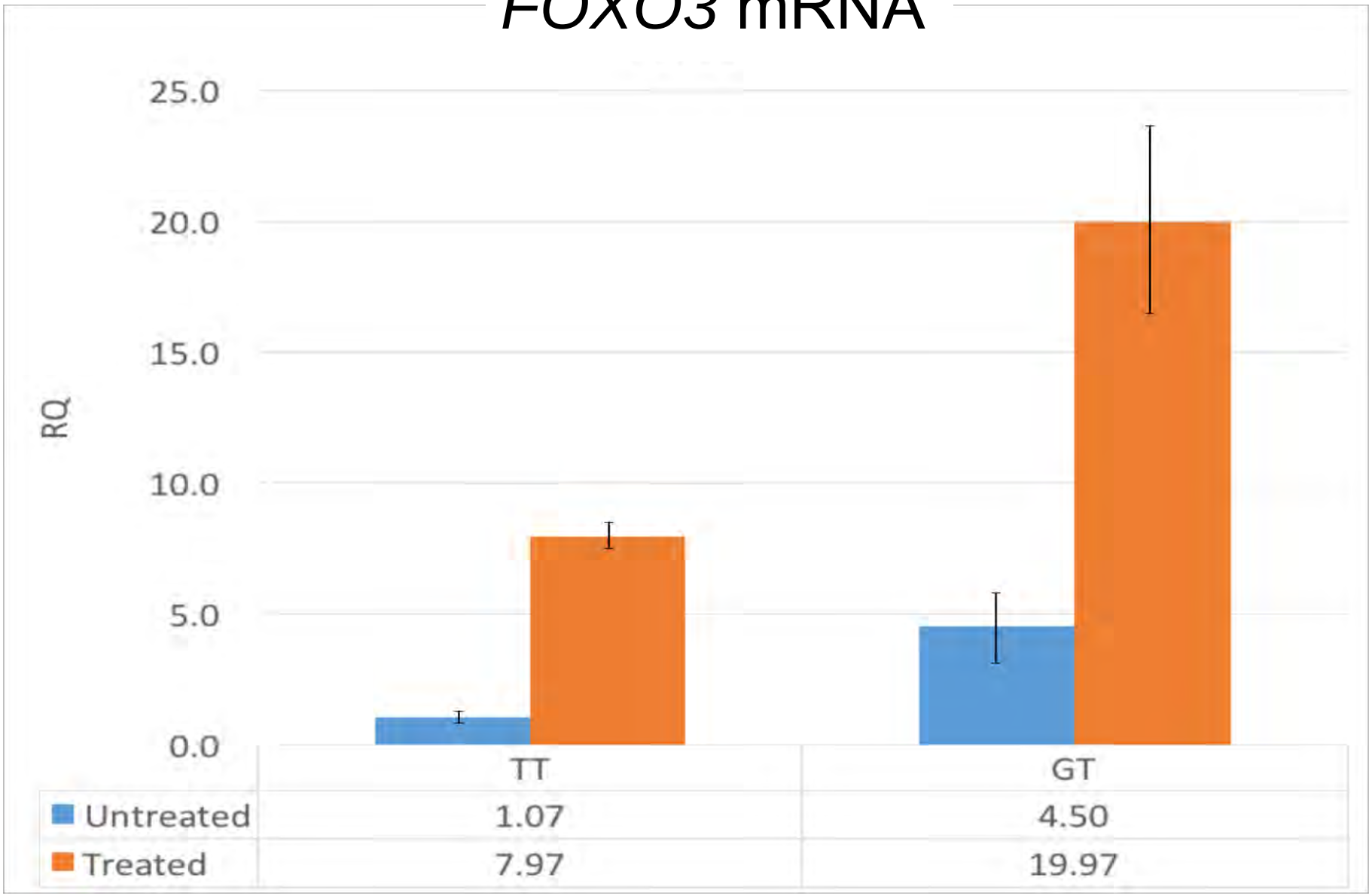
(n = 10 for each genotype and treatment; $P < 0.0001$)







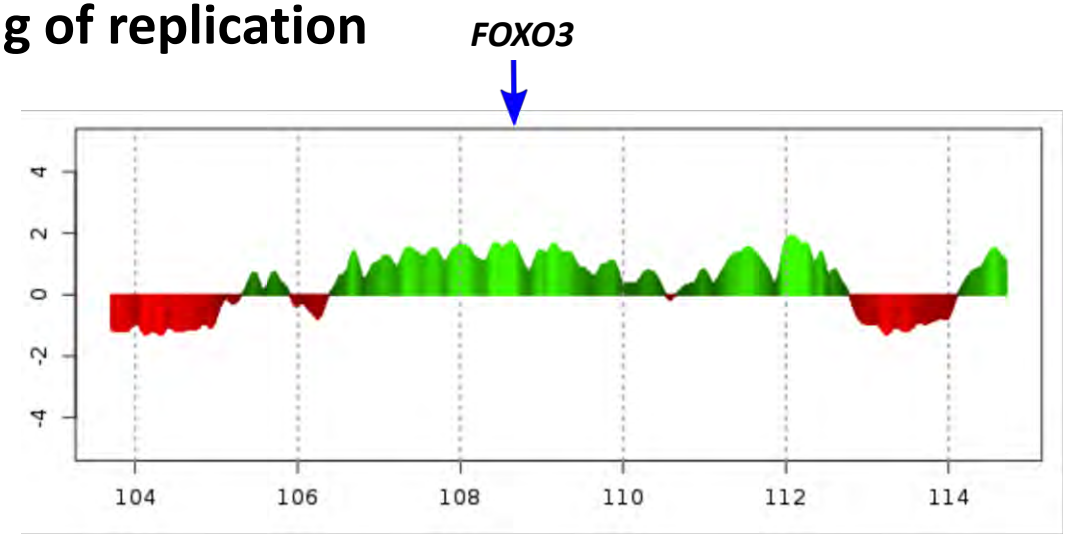
FOXO3 mRNA



	TT	GT
Untreated	1.07	4.50
Treated	7.97	19.97

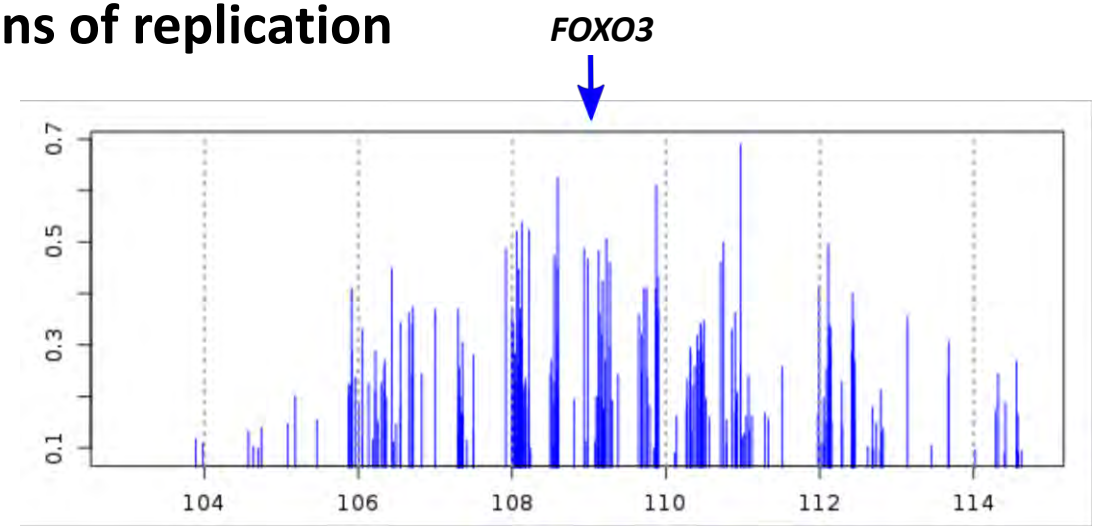
DNA replication of 7.3 Mb region of chromosome 6q21

- **Timing of replication**



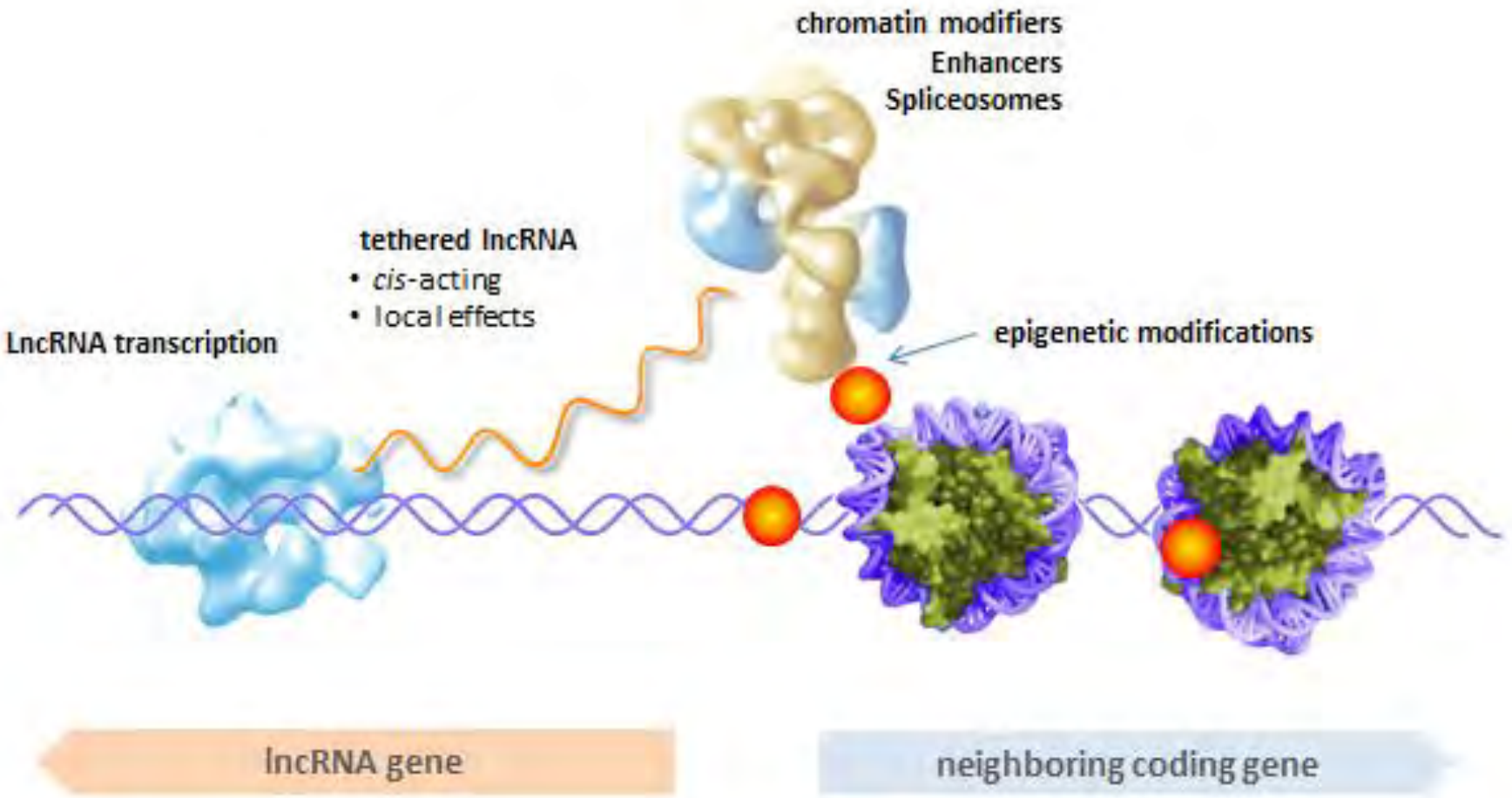
Green = early replicating

- **Origins of replication**



Blue bars = origins of DNA replication

Long noncoding RNAs



Long noncoding RNAs in the *FOXO3* region

- We mapped 626 long non-coding RNAs (lncRNAs) to the 6q21 region
- These included lncRNAs at genes *WISP3* and *TUBE1*
- One, *LINC00222,* appeared to be connected with the *FOXO3* promoter and *FOXO3* longevity-associated SNPs via RNA polymerase II binding
- We hypothesize that at least some of these lncRNAs may be involved in *FOXO3* interactions and formation of the complex with neighbouring genes

Omnigenic model

Boyle *et al*. *Cell* 2017

• Hypothesis: Complex polygenic traits are caused by miniscule contributions from a vast number (~100,000) of sufficiently interconnected peripheral DNA variants that affect core disease genes in relevant tissues.

• These may include transcriptional networks, post-translational modifications, protein-protein interactions, and intracellular signalling.

• Since the peripheral genes exceed core genes by 100:1, they make a large contribution to the trait.

Therefore, could gene-gene interactions, as we showed for the *FOXO3* "gene factory", represent a novel facet of the omnigenic model? [Morris, *Circ Cardiovasc Genet 2017*]

FOXO3 summary

- Protective genotypes of *FOXO3* have higher transcription because they form distinct conformations within the gene itself and between neighbouring genes
- *FOXO3* is at the hub of an interacting set of genes on chromosome 6 involved in cell protection and healthy ageing
- Reduces risk of death from cardiovascular disease in particular
- The cluster represents a longevity 'gene factory'
- This concept may accord with the omnigenic theory that may explain the 'missing heritability' of GWAS
- Adds to well-known effects of FoxO3 transcription factor on expression of a wide array of genes genome-wide

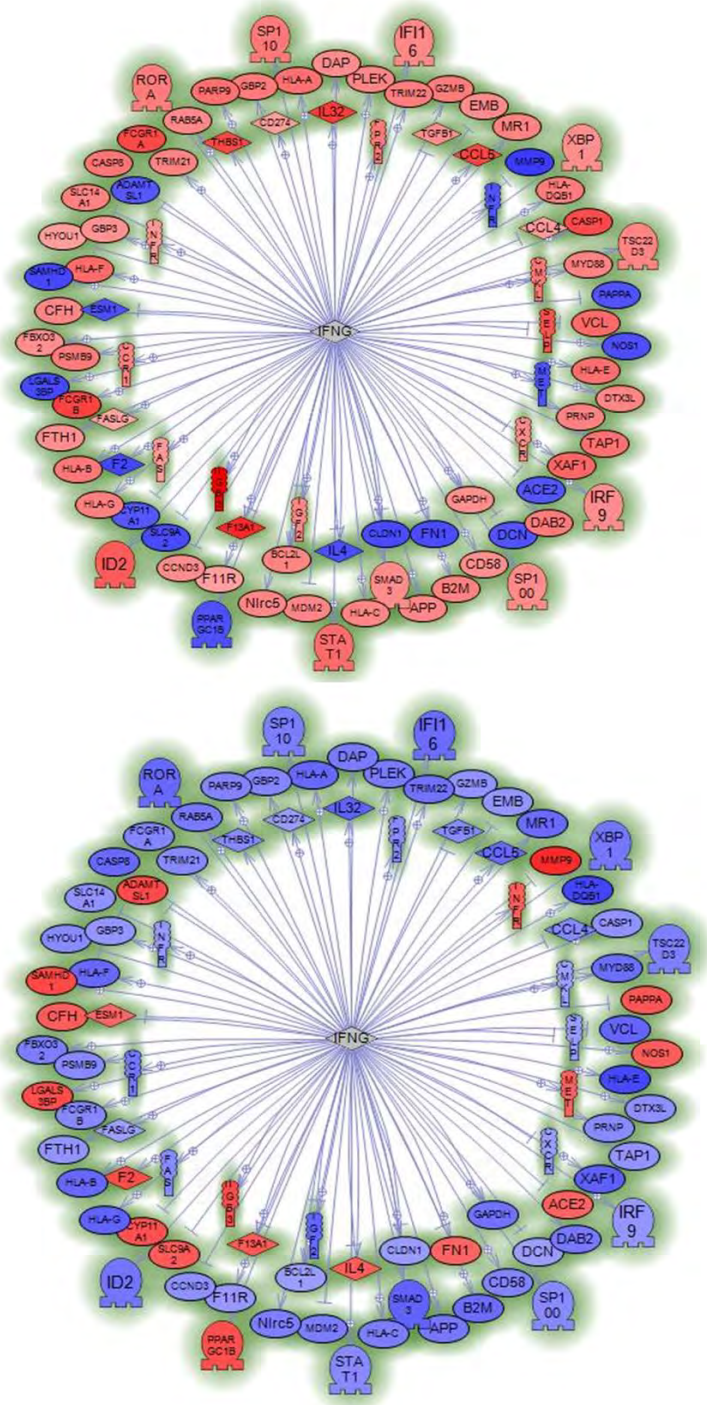
TRANSCRIPTOMICS

- The transcriptome of centenarians differs from septuagenarians and young people
- 1,721 genes are differentially expressed cf. young people
- Most statistically significant:

  immune response, cell adhesion, MHC class 1 receptor activity, transport processes, antigen processing and presentation of peptide antigen via MHC class 1, response to drug, ion transport, signal transduction, cell surface receptor linked signalling pathway, small GTPase mediated signal transduction, intracellular signalling pathway, response to wounding, presentation of endogenous peptide antigen, response to hypoxia, apoptosis, protein transport, T cell activation, processes integral to the plasma membrane

Centenarians vs. young

Example of sub-network analysis for one of the 6 genes that were prominent: **interferon-γ gene: *IFNG***. Shown are genes regulated by *IFNG* in mononuclear cells from centenarians and septuagenarians as compared with young individuals [Borras *et al*. *Aging* 2016]



Septuagenarians vs. young

SUMMARY

- Numerous genes having SNPs associated with longevity
- Protein-protein interaction networks – the ‘gerontome’
- Gene-gene interaction network – *FOXO3* ‘gene factory’ (Other ‘gene factories’ likely)
- Transcriptomics – gene expression networks

Review article published on 2 Sep 2018: Morris *et al*. *BBA*: preprint available online

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FUNCTION

Mitogen-activated kinase kinase kinase 5 (MAP3K5/ASK1)

- cell differentiation and survival, apoptosis, innate immune response, oxidative stress response
- klotho (an ageing suppressor) downregulates the ASK1 signalosome (a ROS-sensitive complex) to reduce p38 MAPK activity and senescence pathways, thus promoting longevity

Fms-related tyrosine kinase gene (*FLT1*)

- encodes vascular endothelial growth factor 1 receptor involved in stimulation of vasculogenesis and angiogenesis
- colorectal cancer survival pathway

Sirtuin 7

- located in nucleolus, binds proteins involved in RNA polymerase I transcription, increases resistance to oxidative stress, maintains number of mitochondria, promotes stem cell survival

Sirtuin 5

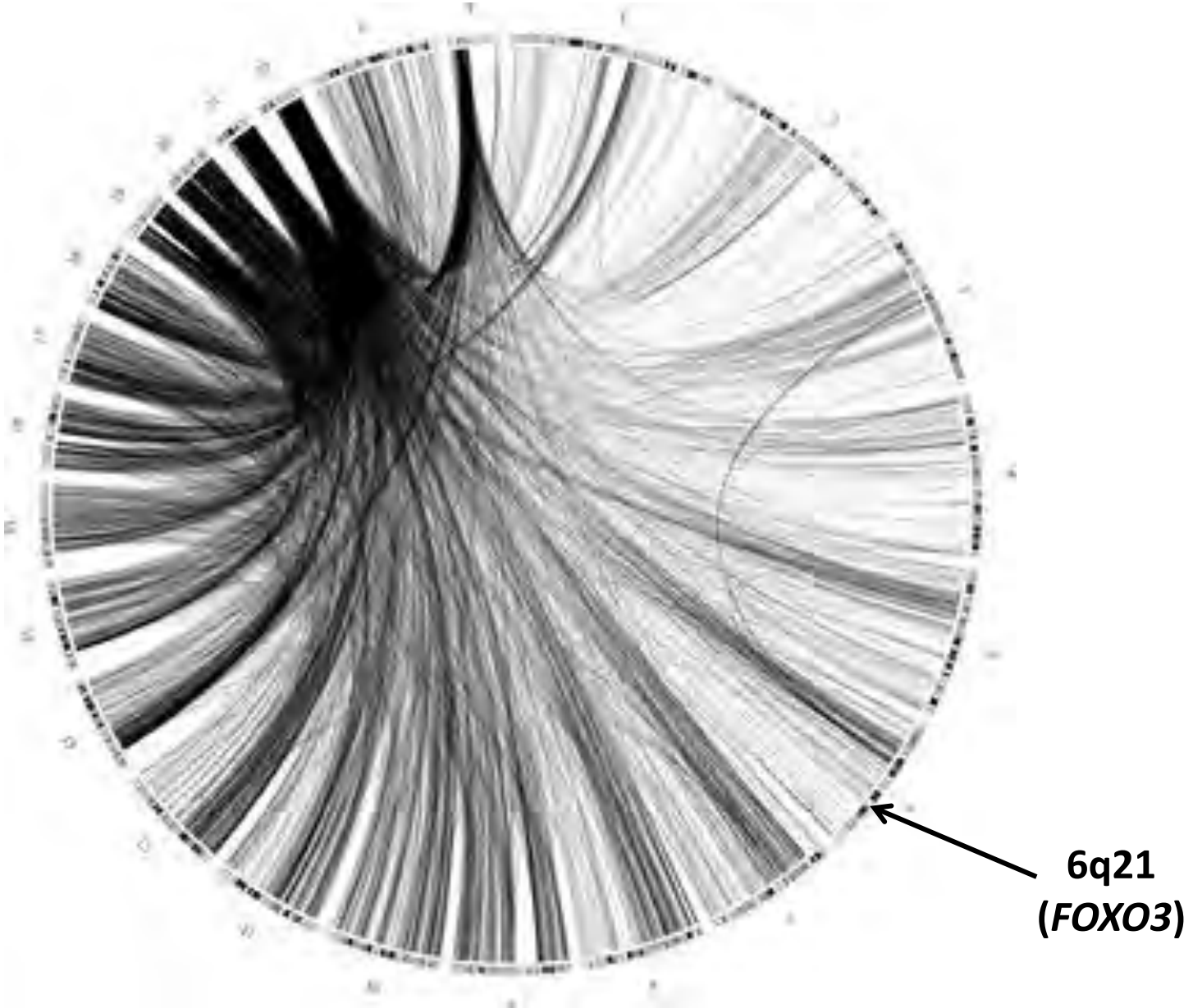
- located in mitochondria, metabolism, detoxification of ammonia
- cardioprotective

(the promoters of *SIRT5* and *SIRT7* are differentially regulated with ageing)

Phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1)

- regulates PI_3 kinase in insulin signalling cascade, downregulation of which is associated with increased lifespan
- the 3 SNPs were associated with body weight and expiratory volume

No apparent interaction of the chr 6q21 (*FOXO3*) region with loci on other chromosomes



Association of tagging SNPs with longevity in those genes with SNPs exhibiting *P* < 0.05 by multiple models

Gene	SNP	Genotype (refer)	Model	OR (95% CI)	*P*	Cases:controls
MAP3K5	*rs2076260*	*CT,TT* (*CC*)	Het disadvan	1.89 (1.41–2.54)	0.0000025*	393:344
SIRT7	*rs34829162*	*GG,TT* (*GT*)	Het disadvan	2.20 (1.52–3.18)	0.0000025*	371:352
SIRT5	*rs2253217*	*TT* (*TC,CC*)	Major recess	2.30 (1.54–3.42)	0.000041*	428:367
PIK3R1	*rs7709243*	*TT* (*TC,CC*)	Major recess	1.63 (1.22–2.18)	0.00083*	421:366
TERT	*rs2853677*	*AA,GG* (*AG*)	Het disadvan	1.66 (1.22–2.24)	0.0011	379:350
TXN	*rs3808888*	*GA,AA* (*GG*)	Minor dom	1.49 (1.13–1.96)	0.0051	437:374
SIRT4	*rs2522134*	*GG,AA* (*GG*)	Het disadvan	1.51 (1.14–2.01)	0.0038	424:366
NR3C1	*rs9324921*	*CC,CA* (*AA*)	Major domin	1.87 (1.20–2.91)	0.0056	438:374
RPTOR	*rs9908495*	*TT* (*TC,CC*)	Major recess	1.51 (1.10–2.07)	0.011	419:346
MAP3K9	*rs7713083*	*TG,GG* (*TT*)	Minor domin	0.69 (0.52–0.93)	0.014	440:374
STAT3	*rs4796791*	*CC,CT* (*TT*)	Major domin	1.50 (1.08–2.08)	0.015	440:374
GHR	*rs4130113*	*AA* (*AG,GG*)	Major recess	1.43 (1.07–1.91)	0.015	440:374
SIRT3	*rs11246009*	*AA,TT* (*AT*)	Het-disadvan	1.44 (1.06–1.96)	0.019	415:362
FLT1	*rs2296190*	*GG,CG,CC*	Additive	1.49 (1.05–2.10)	0.024	420:366
SIRT1	*rs4746720*	*TT* (*TC,CC*)	Major recess	1.41 (1.01–1.92)	0.026	408:356
JAK2	*rs3824432*	*AA* (*AG,GG*)	Minor recess	2.79 (1.10–7.07)	0.030	433:371
SIRT2	*rs10405150*	*CC* (*CT,TT*)	Minor recess	3.95 (1.12–14.0)	0.033	409:364
TFDP1	*rs11839469*	*GC,CC* (*GG*)	Minor domin	1.55 (1.03–2.33)	0.036	440:374

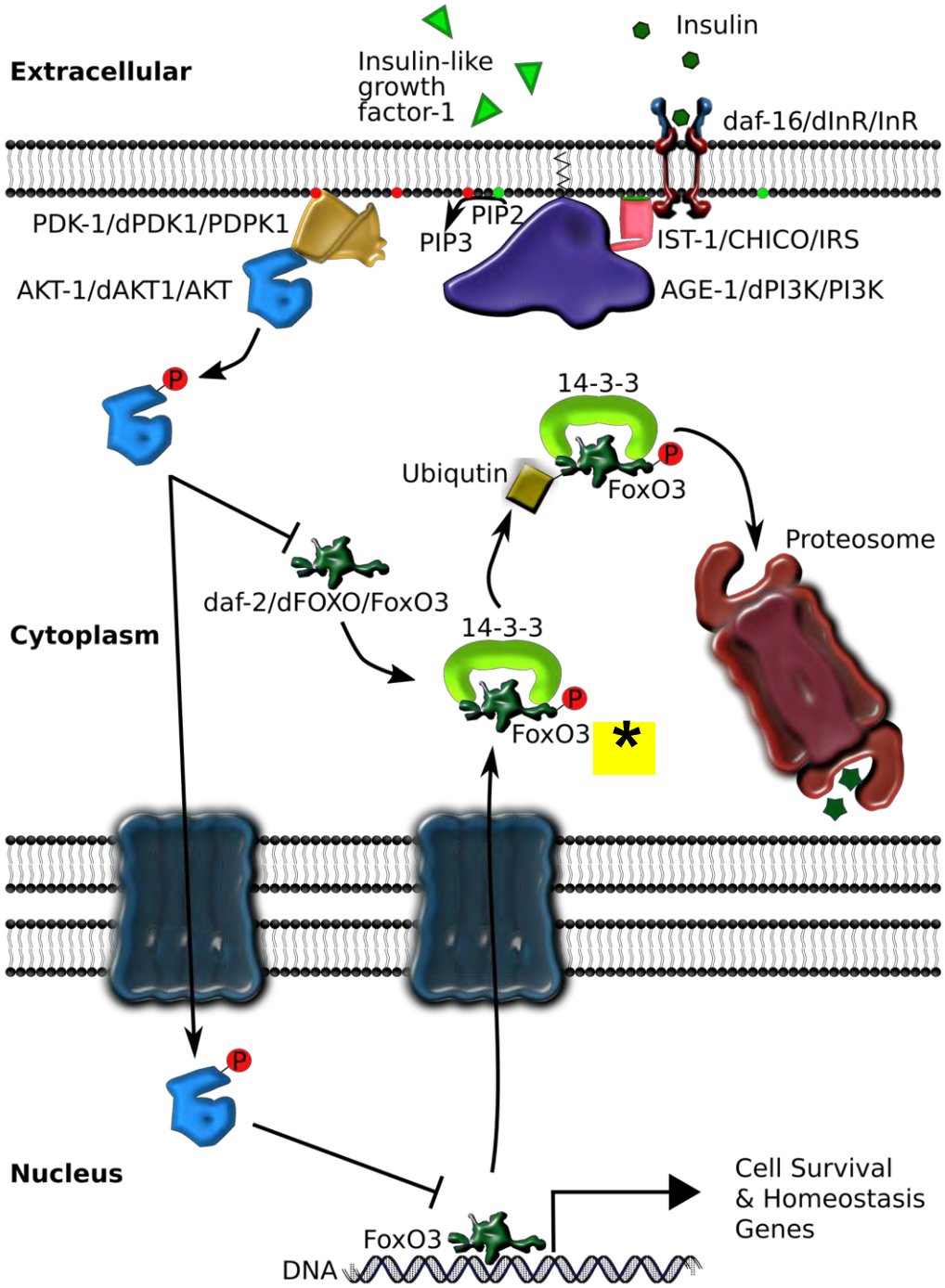
*Significance retained after Bonferroni correction

Alphabetical list of genes showing number of SNPs tested in each, those SNPs that were associated with longevity at the *P* < 0.05 level using a dominant model, and those SNPs that were adjacent to each othe

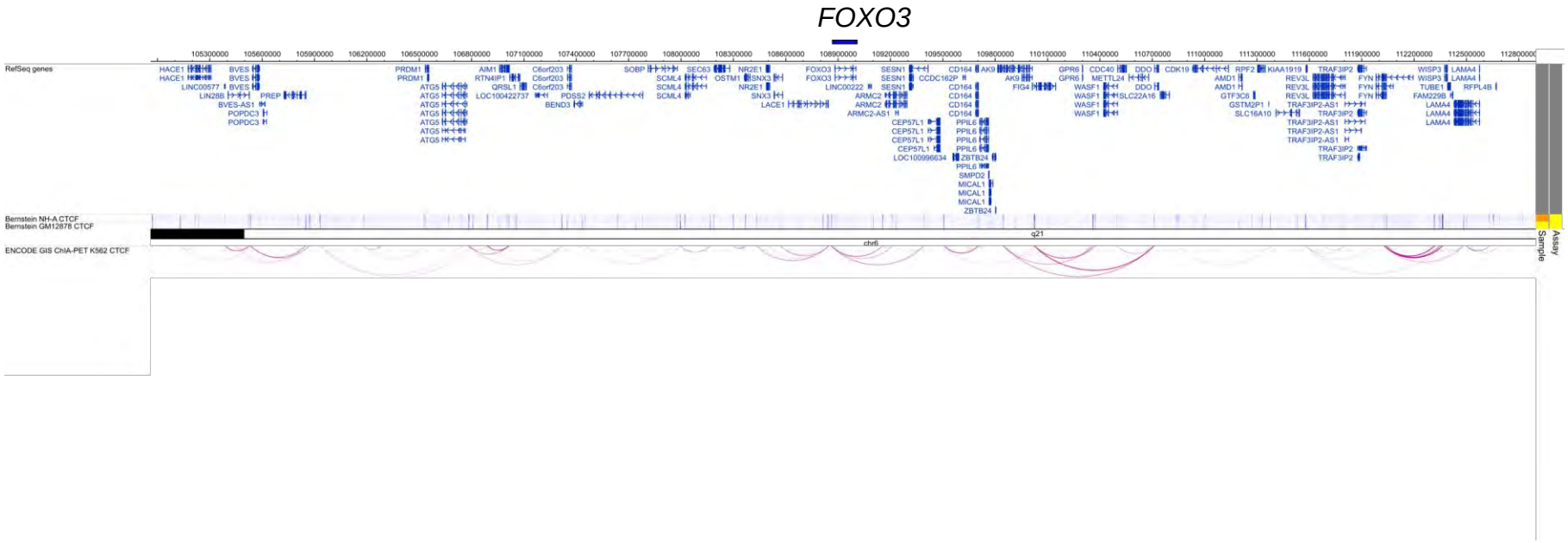
Gene	No. tSNPs tested	Statistically significant tSNP(s) and *P* value	Adjacent?
FTL1	42	***rs3794396*** (*P*=0.0007) ***rs7987649*** (*P*=0.019) ***rs9513099*** (*P*=0.025)	All adjacent
GHR	14	***rs4130113*** (*P*=0.015)	
MAP3K5	34	***rs2076260*** (*P*=0.0043) ***rs6904753*** (*P*=0.032)	Adjacent
MAPK9	17	***rs7713083*** (*P*=0.013)	
NR3C1	18	***rs2963155*** (*P*=0.023)	
PIK3R1	19	***rs7709243*** (*P*=0.0008) ***rs7713645*** (*P*=0.0041) ***rs6881033*** (*P*=0.0057)	All adjacent
RPTOR	65	***rs9908495*** (*P*=0.011)	
SIRT1	4	***rs4746720*** (*P*=0.026)	
SIRT5	7	***rs2253217*** (*P*<0.0001)	
SIRT7	2	***rs34829162*** (*P*=0.0031)	
TERT	13	***rs2853676*** (*P*=0.016)	
TFDP1	5	***rs11839469*** (*P*=0.036)	
TXN	8	***rs3808888*** (*P*=0.0051)	

Results of haplotype analysis for the 3 genes having adjacent longevity-associated SNPs

Gene	SNP	*P value*
MAP3K5	*rs6904753-C*	0.032
	rs2076260-T	0.0043
	Haplotype: *CT*	<0.0001
FLT1	*rs3794396-C*	0.0007
	rs7987649-G	0.019
	rs9513099-C	0.025
	Haplotype: *CGC*	0.00050
PIK3R1	*67527326-C*	0.0041
	67529191-A	0.0056
	67534039-T	0.0008
	Haplotype: *CAT*	0.58


Extracellular
Insulin-like growth factor-1
Insulin
daf-16/dInR/InR
PDK-1/dPDK1/PDPK1
PIP2
PIP3
IST-1/CHICO/IRS
AKT-1/dAKT1/AKT
AGE-1/dPI3K/PI3K
P
14-3-3
Ubiqutin
FoxO3
Proteosome
daf-2/dFOXO/FoxO3
Cytoplasm
14-3-3
FoxO3
*
Nucleus
Cell Survival & Homeostasis Genes
FoxO3
DNA

Long-range CTCF* chromatin contacts between promoter of *FOXO3* and neighbouring genes in a 7.3 Mb region of chromosome 6q21



*CTCF = CCCTC-binding factor zinc finger protein

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GENOTYPING

High-throughput genotyping on universal bead arrays (Illumina GoldenGate platform) of 459 tSNPs in the 58 genes

The gene *FOXO3* interacts with its neighbors in a 46-gene cell resilience “gene factory” on chromosome 6q21 [80].
Upper panel: fluorescent *in situ* hybridization experiments showing, on the *left*, in quiescent lymphoblastoid cell lines *right*, change in position of the genes in cells after activation by stress, induced by serum deprivation and H_2O_2 treatment.
Lower panel: schematics showing the effect; for simplicity only 5 of the 46 neighborhood genes are shown.
The sphere denotes a presumed transcription center.